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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Rec'd PCT/PTO 28 FEB 2005

Applicant's or agent's file reference LRD-PCT-421		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/BE 03/00144		International filing date (day/month/year) 01.09.2003	Priority date (day/month/year) 30.08.2002
International Patent Classification (IPC) or both national classification and IPC A61K38/14			
Applicant K.U. LEUVEN RESEARCH AND DEVELOPMENT et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 11 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the opinion</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input checked="" type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand 29.03.2004		Date of completion of this report 11.11.2004	
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Kronester-Frei, A Telephone No. +49 89 2399-8555 	

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International application No. **PCT/BE 03/00144**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-72 as originally filed
26a received on 08.10.2004 with letter of 08.10.2004

Claims, Numbers

1-21 received on 08.10.2004 with letter of 08.10.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
 - ☐ the entire international application,
 - ☒ claims Nos. 17,18
because:
 - ☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos.
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
 - ☐ the written form has not been furnished or does not comply with the Standard.
 - ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:
 - ☒ restricted the claims.
 - ☒ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
 - ☒ complied with.
 - ☐ not complied with for the following reasons:
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

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- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-21 .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-21
	No: Claims	
Inventive step (IS)	Yes: Claims	1-21
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-17,20,21
	No: Claims	18,19

2. Citations and explanations

see separate sheet

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Re Item I

Basis of the opinion

Reference is made to the following document/s/:

- D1: International Journal Of Antimicrobial Agents (12-2001), 18(6), 513-518
- D2: Journal Of Natural Products. United States Jul 2001 (07-2001), 64(7), 874-882
- D3: Medicinal Research Reviews, New York, Ny, Us (1997), 17(1), 69-137
- D4: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 46, no. 8, August 2002 (2002-08), pages 2344-2348, ISSN: 0066-4804
- D5: EP-A-0365319
- D6: EP-A-0667353
- D7: WO-A-0181372
- D8: WO-A-0158933
- D9: WO-A-0069893
- D10: BORGHI A ET AL: 'MICROBIAL DE-MANNOSYLATION AND MANNOSYLATION OF TEICOPLANIN DERIVATIVES' JOURNAL OF ANTIBIOTICS, JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO, JP, vol. 44, no. 12, December 1991 (1991-12), pages 1444-1451, XP009023200 ISSN: 0021-8820
- D11: MALABARBA A NICAS TI CIABATTI R: 'Glycopeptide resistance in multiple antibiotic-resistant Gram-positive bacteria: a current challenge for novel semi-synthetic glycopeptide derivatives' EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 32, no. 6, 1 June 1997 (1997-06-01), pages 459-478, XP004088458 ISSN: 0223-5234
- D12: MALABARBA A ET AL: 'TEICOPLANIN, ANTIBIOTICS FROM ACTINOPLANES TEICHOMYCETICUS NOV. SP. VII. PREPARATION AND NMR CHARACTERISTICS OF THE AGLYCON OF TEICOPLANIN' JOURNAL OF ANTIBIOTICS, JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO, JP, vol. 39, no. 10, October 1986 (1986-10), pages 1430-1442, XP009025778 ISSN: 0021-8820
- D13: EP-A-0 276 740 (LEPETIT SPA) 3 August 1988 (1988-08-03)
- D14: US-A-5 500 410 (MALABARBA ADRIANO ET AL) 19 March 1996 (1996-03-19)
- D15: US-A-5 521 155 (MALABARBA ADRIANO ET AL) 28 May 1996 (1996-05-28)

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

For the assessment of the present claims 18, 19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item IV

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The regrouping of the 3 inventions as identified by the International Search Authority could establish the common inventive concept which is in line with the requirements of unity of the invention. In fact the tuning at the antibiotic positions 7b of the glycopeptide antibiotics according to formula I and II seem to be the core modification, however the structural context of the whole molecule seems to be essential also.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- D1: Cancer chemotherapy + antiviral therapy positive for ==> lymphomas in HIV-infected patients. Since the nucleic acid binding chemotherapeutic agent bleomycin in itself has antiviral properties, discovered synergy with current anti-HIV agents. Combinations of zidovudine, indinavir or ritonavir with bleomycin, synergistically inhibited HIV-1AT replication. HIV (Retroviridae)
- D2: The natural peptide antibiotics as there are complestatin derivatives, isocomplestatin, chloropectin I can act as HIV-I Integrase Inhibitors, which is known to be the responsible enzyme for virus replication. Some structural subunits are similar to vancomycin.
- D3: General modification strategy of glycopeptide antibiotics, overview
- D4: Alkylation of the 4-epi-vancosamine moiety of the dissaccharide significantly enhances the antibacterial activity of the hexapeptide, can effect dimerization and binding to bacterial membranes. Works by binding to the l-Lys-D-Ala-D-Ala cell wall analog.
- D5: epi-vancosamyinyl derivatives of vancomycines, antibacterial activity, against Gram-positive microorganisms.
- D6: Vancomycin-derivatives, antibiotic activity, mainly against different strains of Staphylococcus.
- D7: Vancomycin-Derivatives with vancosamine modification, treatment of infections that are resistant to antibiotics.
- D8: N-Alkylation derivatives of vancomycin with antimicrobial activity
- D9: Vancomycin analogs having a vancosamine residue which is substituted with a lipid-like substituent, improved solubilities, antimicrobial activity
- D11: Resistance to the glycopeptide antibiotics teicoplanin (T) in multi-resistant Gram-positive pathogens, particularly enterococci, is becoming a dramatic nosocomial problem non-natural glycopeptides in which amino acids 1 and 3 are replaced by new amino acids have been prepared
- D12: Hydrolytic reactions that transform teicoplanin or its pseudo-aglycones into the aglycone with good yields
- D13: N<1><5> mono-or di-alkyl derivatives of teicoplanin antimicrobial activity in particular against gram positive bacteria.
- D14: C63 amide derivatives of teicoplanin wherein the amide moiety is derived from a di-or poly-alkylamine, amide derivatives of the invention are active against gram positive and gram negative bacteria
- D15: Teicoplanin amides broad-spectrum antibacterials esp. effective against gram-positive strains

1. The amended set of claims does not introduce which extends beyond the content

of the application as filed, therefore Article 19(2)/Article 34(2)(b) PCT is satisfied.

2. With respect to the prior art cited in the Int. Search Report novelty of the subject-matter claimed can be acknowledged.
3. Also the exemplified vancomycin derivatives of claim 11 and dependent subject-matter in claims 13 and 17 (second medical use) is considered to be novel together with their related first medical use claims 13 and 14.
4. The content of the present application relates to the use glycopeptide antibiotics, which were generally known to be useful in bacterial infections, for treatment/prevention of viral infections. In particular disclosed derivatives of vancomycin, teicoplanin, eremomycin, chloreremomycin, de chloroeremomycin, ristomycin, DA40926 and Demannosyl-DA40926. Activity against HIV, HCV, SARS, HSV-1, HSV-2, CMV, VZV, FCV, BVDV.

As far as the requirements of inventive step of claims 1-19, 22 are concerned it would appear that a person skilled in this art confronted with the problem of looking for further antiviral agents being based on a glycopeptide antibiotic structure would in principle have been able to conclude in an obvious manner from the teaching of D1 to D4 that the basic structure of vancomycin derivatives would open an interesting field for testing different embodiments for their antiviral activity.

However the selection of the tuning moiety in nucleus 7a seems to be reflect the result of the presence of inventive activity; in addition the tests provided in the applications as originally filed establish the presence of antiviral activity like anti-HIV (Examples 5-7), antiviral activity against BVDV, HCV, HSV, VCV, CMV, FCV, SARS (Examples 8-13).

However, the extent of generalization made in the claims 1 - 3, 9 -10 seems to include speculative elements since it does not seem to be reasonable to expect that the glycopeptide derivatives would act as an antiviral agent over the whole field covered by the rather general family terms and/or general Markush formula.

With the information at present in this file the requirements of inventive step are rendered plausible for the examples made and the related field of generalization around them.

In this context it would appear that the teaching of claims 20 and 21 necessarily should be made dependent from structure claims.

5. Claims 20 to 21 typically are written in the so-called reach-trough structure which is not considered to satisfy the requirements of Article 5/6PCT.

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6. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 - D15 is not mentioned in the description, nor are these documents identified therein.